ABSTRACT

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Title of Thesis: 2,4-Disubstitued quinazolines as potential ligands for CAR receptors

CAR (constitutive adrostane receptor) is a nuclear receptor that has an impact on cell metabolism. It is a negative regulator of lipid metabolism (via liponeogenesis inhibition), β-oxidation of fatty acid, and gluconeogenesis. This receptor also plays an important role in metabolism of exogenous and endogenous toxins.

After revealing the fact that 2-(3-methoxyphenyl)quinazoline-4-ol may act as a ligand for CAR we focused on a synthesis of a small library of its derivatives.

The synthesis of desired quinazoline was carried out in three steps with very good overall yield. The first group of 4-alkyloxy-2-(3-methoxyphenyl)quinazolines was prepared by simple alkylation reactions with alkylhalogenides. The second group of (4-alkylsulfanyl-2--(3-methoxyphenyl)quinazolines) was synthesized by reaction with phosphorus pentasulfide followed by reaction with methyl iodide. The most recent group of derivatives, (4-alkylamino-2-(3-methoxyphenyl)quinazolines), was synthesized by nucleophilic substitution of 4-fluorobenzenesulfonated intermediate with appropriate amine leading to desired product with satisfactory yields. Attempts to synthesize the fourth series of compounds possessing methoxy fragment shifted to position 4 on the phenyl moiety employing a coupling reaction with a direct activation of a C-H bond were unsuccessful.

All prepared compounds were submitted for an investigation of the affinity to CAR receptors.